IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Juan MANTELLE et al.

Title: COMPOSITIONS AND METHOD FOR TREATMENT OF ATTENTION DEFICIT DISORDER AND ATTENTION DEFICIT/HYPERACTIVITY DISORDER WITH METHYLPHENIDATE

Appl. No.: 10/024,513

Filing Date: December 21, 2001

Examiner: F. Choi

Art Unit: 1616

DECLARATION UNDER 37 C.F.R. § 1.131

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. This Declaration is submitted to establish completion of the invention recited in the claims of this application in the United States, on a date before February 15, 2001, which I am told is the effective prior art date of WO 01/10420 (hereinafter "Vickers") under § 102(a)/103(a) of the patent laws. I understand that Vickers was cited by the Examiner in an Office Action dated December 15, 2003, in the above-identified application. The person making this declaration is one of the two joint inventors of the captioned application.

FACTS AND DOCUMENTARY EVIDENCE

2. A clinical study sponsored by Noven Pharmaceuticals, Inc. ("Noven") was conducted and completed in the United States to quantify and compare the pharmacokinetics and delivery release of methylphenidate from a transdermal drug delivery system versus an oral formulation (Ritalin®). See Exhibit 1 ("The Study"). This study supports a New Drug Application (NDA)

filed with the Food and Drug Administration (FDA). The NDA seeks approval to market a transdermal drug delivery system for delivering methylphenidate for the treatment of attention-deficit hyperactivity disorder (ADHD).

3. The transdermal drug delivery systems tested in The Study were manufactured and packaged at Noven. The composition of the tested transdermal systems corresponds to Example 1, Paragraph [0050] of the present application as described in Exhibit 2.

4. Specifically, the composition of the tested transdermal systems comprised 20 wt% methylphenidate, 40 wt% BIO-PSA 7-4102, and 40 wt% Gelva 3087. See Exhibit 2. BIO-PSA 7-4102 is a silicone adhesive, and Gelva 3087 is an acrylic adhesive. The composition was substantially free of ritalinic acid at the time of manufacture and comprised no more than about 5% weight/weight of acid functional monomers. The composition was formulated as a flexible, finite system for topical administration, as noted in paragraph [0050] of the present application.

5. The Study design and methods are summarized in paragraph [0052] of the present application.

6. Pharmacokinetic parameters were calculated from the plasma data collected from The Study. The mean time-plasma concentration profiles calculated from The Study plasma data are graphically presented in Exhibit 3 which corresponds to Figure 1 of the present application.

7. The plasma profiles of methylphenidate are described in Exhibit 3 using a graph with time in hours on the x-axis and methylphenidate plasma concentration in nanograms per milliliter (ng/mL) on the y-axis. As can be observed on the graph, patients administered methylphenidate in the form of a transdermal patch had a plasma concentration of methylphenidate of about 2 ng/mL at the initial time point. This plasma concentration steadily increased to a maximum of about 8 ng/mL at around 8 hours. Once reaching this maximum concentration, the methylphenidate plasma concentration steadily decreased to return to the about the starting concentration of 2 ng/mL at 28 hours.

8. The increase in the methylphenidate plasma concentration can also be expressed as a rate of increase. This rate of increase in methylphenidate plasma concentration can be calculated

based on the data presented in Exhibit 3 as an increase in methylphenidate plasma concentration in ng/mL per hour. For example, the plasma concentration of methylphenidate increases from about 4 ng/mL to about 7 ng/mL between hours 4 and 8. Thus, the rate of increase is 0.75 (ng/mL)/hr. Selecting different time points will yield slightly different rates, but a rate of increase of about 0.75 (ng/mL)/hr is representative of the rate of increase demonstrated in Exhibit 3. The graph demonstrates a methylphenidate delivery of at least 5 mg per 24 hours.

9. As taught in the present application, a delivery rate of about 0.5 mg/24 hours to about 100 mg/24 hours is needed to achieve a therapeutically effective dose. Specification, pg. 15. Exhibit 3 shows that the tested composition delivers a therapeutically effective amount of methylphenidate over a period of time of about 12 to about 24 hours, and indeed delivers a therapeutically effective amount over a period of about 12 to about 18 hours.

10. In summary, Exhibit 3 demonstrates a composition that delivers methylphenidate in an amount and rate sufficient to increase the methylphenidate plasma concentration of a subject being treated over a period of about 6-16 hours, followed by a steady decrease in the plasma concentration of methylphenidate.

11. Reference to dates have been deleted from the Exhibits to preserve the actual reduction to practice date in confidence. However, the Declarant certifies that the examples were actually reduced to practice, The Study was performed, and The Study data collected and analyzed, before February 15, 2001. Therefore, Declarant believes that he was in possession of the whole claimed invention before February 15, 2001.

CONCLUSION

12. The clinical study was completed, and the plasma data collected and analyzed as described in the Exhibits, before February 15, 2001. The invention of the present application was actually reduced to practice before February 15, 2001.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Date: June 15, 2005

By: _____
Juan A. Mantelle

FINAL INTEGRATED STUDY REPORT

A MULTIPLE-DOSE PHARMACOKINETIC STUDY OF A METHYLPHENIDATE TRANSDERMAL SYSTEM COMPARED TO RITALIN® IN HEALTHY ADULT SUBJECTS

PROTOCOL NUMBER: [redacted]

Name of Drug:	Methylphenidate
Indication:	Attention-deficit hyperactivity disorder (ADHD)
Study Design:	Open-label, randomized, multiple-dose, two-way crossover study
Sponsor:	Noven Pharmaceuticals, Inc. 11960 SW 144th Street Miami, FL 33186
Name of Sponsor Signatory:	[redacted]
Drug Development Phase:	I
Study Initiation Date:	[redacted]
Study Completion Date:	[redacted]
Principal Investigator:	[redacted]
Report Date:	[redacted]

The study was completed according to the guidelines of Good Clinical Practice (GCP) and was conducted in full compliance with the World Medical Assembly Declaration of Helsinki and its most recent amendments at:

South Florida Bioavailability Clinic
11190 Biscayne Boulevard
Miami, Florida, 33181

PRODUCT PROFILE SHEET

CONFIDENTIAL

Product: Methylphenidate, CII

Formulation No. 6

Code No.	Ingredient	% w/w Wet	[redacted]	[redacted]	% w/w in Finished Dry Product
N244	Gelva 3087 *	53.33	[redacted]	[redacted]	40.00
N229	BIO-PSA 7-4102 *	33.33	[redacted]	[redacted]	40.00
N201	Ethyl Acetate	3.08	[redacted]	[redacted]	0.00
N245	Methylphenidate Base	10.255	[redacted]	[redacted]	20.00
*Formulation % w/w Wet is based on the theoretical % solids					
	Total	100.00	[redacted]	[redacted]	100.00

Patch Size = 6.25, 12.5, 18.75, 25 cm²

[redacted]

Performed By/Date: [redacted] Checked By/Date: Melissa S [redacted]

Blend Code No: [redacted]

Laminate Code No: [redacted]

Packaging Code No: [redacted]

[redacted] Code No's Issued By/Date: [redacted]

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Figure1 Mean (linear) *d*-MPH plasma profiles in 29 subjects on Day 6 after administering 25cm^2 MTS units every 24 h (MTS) for 16 h or 20 mg oral Ritalin® at 7 AM, 11 AM and 3 PM daily (Ritalin®).